ANNALS OF PHYSICAL MEDICINE

The Official Organ of the
BRITISH ASSOCIATION OF PHYSICAL MEDICINE

Vol. IV November 1957 No. 4

REVISION SERIES

STEROID THERAPY

BY J. H. GLYN AND D. R. L. NEWTON

From the Department of Physical Medicine and Rheumatism, The Middlesex Hospital, and the Department of Physical Medicine, St. Thomas's Hospital, London

THE field of steroid therapy is so vast that a complete review would be impossible in a short article of this nature, which is intended to help the clinician in his daily practice in the department of physical medicine. This review will therefore be restricted largely to publications which have appeared since the end of 1953, this empirical date-line being chosen partly because it neatly bisects the eight years which have elapsed since the clinical effects of cortisone were first announced in 1949, and partly because the last four years have naturally given rise to more mature research than the early years. There were many excellent review articles and clinical descriptions written during this period, however, and the reader is referred to the following selection: Hench *et al.* (1949), Hench (1952), these being mainly historical; Copeman *et al.* (1954), Boland (1952a), Brochner-Mortensen and Fischer (1953), Ward *et al.* (1953), for a clinical approach; and for mainly metabolic details Ingle (1950), Sprague (1951), and Thorn *et al.* (1950).

The steroid preparations in common use in this specialty are confined almost entirely to those given systemically and those given by intra-articular or local soft-tissue injection. In these days so many proprietary preparations are available that the reader is strongly recommended to acquire the habit of using only the approved name when prescribing, as this prevents error and avoids the need for memorizing proprietary names which may be misleading in their implications.

SYSTEMIC THERAPY IN RHEUMATOID DISEASE

Controlled Trials in Britain

A pertinent, if depressing, starting-point for a discussion of these conditions is furnished by the results of three prolonged but carefully controlled therapeutic trials in which the value of cortisone was compared with that of salicylates given in high dosage. Two of these were multicentre trials in adults organized respectively by the Medical Research Council and Nuffield Foundation (1955) and the Empire Rheumatism Council (1955); the third, also organized by the M.R.C. (Ansell *et al.*, 1956), was carried out largely at one centre and was concerned exclusively with juvenile rheumatoid arthritis. The first of these trials specifically investigated *early* cases of rheumatoid arthritis, patients having complained of symptoms for more than three and less than nine months. The Empire Rheumatism Council included in its trial any patient between the ages of 17 and 60, provided that irreversible joint damage was not too advanced, that there were no specific contraindications to steroid therapy, and that there seemed to be a real chance of improvement. For inclusion in the third trial children had to be under 16 years of age and to have had the disease for less than nine months.

In all three trials the cortisone and aspirin groups were carefully paired and the drug selection was dictated entirely by the central statistician, but in none was the trial "blind" in the strict sense. In each case the results failed statistically to show any significant advantage of the new drugs over the old at the end of one or two years. The recently published results of the M.R.C. trial to the end of four years (Medical Research Council, 1957a) confirm this.

These results, remarkable in their uniformity, have been criticized on technical grounds, especially by those who believe that the available methods of assessing the progress of patients suffering from rheumatoid disease are crude and unrealistic (Smart, 1956; Loxton, 1956; Hart *et al.*, 1954; Glyn, 1954; Hill, 1954; Ehrenberg, 1954). Several efforts have been made recently to standardize methods of assessment, notably by a committee of the American Rheumatism Association (Steinbrocker *et al.*, 1949) and by Lansbury (1956) in Philadelphia, but a satisfactory formula has yet to be found. Nevertheless these three reports appear to be the only examples of authentically controlled trials amongst the many uncontrolled ones which have been published, and therefore they deserve careful appraisal.

Other Investigations

Other reports of prolonged maintenance treatment give a more hopeful picture. Of these one of the largest was the retrospective study conducted by the

American Rheumatism Association (1955) in which 29 specialist clinics co-operated, providing data on 546 patients. The committee freely acknowledged the many substantial pitfalls in drawing deductions from this type of retrospective study (Mainland, 1955), but their conclusions are worth noting. At the end of the study in 1955, 432 of the original 546 patients remained under observation, and of these 60 per cent. were still receiving cortisone. Major undesirable side-effects had occurred in 46 per cent., and minor side-effects in 72 per cent. Rheumatoid nodules and associated psoriasis did not appear to be affected. Functional improvement was consistently greater than grades of response as defined by the Steinbrocker Committee (Steinbrocker *et al.*, 1949), and patients who were mildly affected fared significantly better than those whose initial classification was in the more advanced categories.

Bunim, Pechet, and Bollet (1955) report their experiences of maintenance therapy in 78 cases (including 9 cases of Still's disease) followed over four years. In 70 per cent. of cases there was unequivocal X-ray evidence of progressive joint destruction, though many of these patients were considered to have benefited when judged by clinical criteria. In 20 per cent. new joints were affected while cortisone was being administered, and the response of subcutaneous nodules did not follow the over-all clinical response. During the first year of treatment 23 per cent. of cases went into remission, but the authors do not believe that this figure necessarily represents an improvement on the expectation of natural remission. Only 6 per cent. failed to derive any benefit at all from the hormone. Although the "salvage rate" was especially impressive in patients who were totally incapacitated at the outset of treatment, the authors consider in retrospect that the improvement obtained in approximately 50 per cent. did not warrant the risks which are inherent in long-term cortisone therapy.

Bauer and Ropes (1956) report less happy experiences in 53 cases. Therapy was discontinued because of a poor response in 12 and psychosis in 3; there were 5 deaths, and in only 4 cases (3 of them in children) did remission occur. Two patients stopped taking the drug because they "thought it was bad for them", but a variable degree of clinical improvement was noted in 72 per cent. of all the cases treated.

Some years ago Ragan stated that "in cortisone therapy all we do is to exchange one pathological state for another", and he entitles his latest clinical report (Howell and Ragan, 1956) "The Course of Rheumatoid Arthritis during Four Years of Induced Hyperadrenalism". In this report he and his co-author discuss the response to long-term treatment of 75 patients (64 with cortisone, 11 with ACTH, and 7 with both) who had been receiving the drugs for from 6 months to 5½ years. They stress how difficult it is to predict in advance

how patients will respond, but were led to conclude that "the use of this form of therapy is a limited but necessary adjunct in the management of certain patients. . . . In cases with rapidly progressive disease the use of steroids may be mandatory."

The following selection of clinical reports on maintenance therapy may be found useful. West and Newns (1955) compare the results of prolonged corticotrophin and cortisone therapy. Toussaint (1955) obtained partial or complete remission in half his cases of rheumatoid arthritis and ankylosing spondylitis with cortisone or hydrocortisone. Hansen *et al.* (1956) in a detailed report conclude that maintenance therapy is of value in more than half the cases treated. Solem and Römke (1956) find that for various reasons only 16 per cent. of over 200 patients with rheumatoid arthritis obtained worthwhile benefit from prolonged treatment with steroids. Toone and Irby (1955) conclude that cortisone is indicated only when other treatment has failed. Kinsell (1954) reports that the "salvage rate" is higher with "suppressive" than with purely "analgesic" steroid dosage. Bilka and Weil (1955) find that there is nothing to recommend treatment with gold and steroids combined. Hench and Ward (1954) give a comprehensive review of clinical experiences up to the middle of 1954.

CORTICOTROPHIN (ACTH)

It is still extremely difficult to obtain a pure extract of corticotrophin, and correspondingly difficult to standardize its potency. Unpleasant anaphylactoid reactions due to contamination with foreign proteins are occasionally produced (Swift, 1954; *Lancet*, 1956), and it is now established that acquired resistance to corticotrophin can develop in the course of prolonged treatment (West, 1956). Specific antibodies have been detected when using the very crude early preparations of corticotrophin, but antibodies to the so-called "highly purified" preparations which are now available have not yet been isolated, though there is much circumstantial evidence that cell-fixed antibodies probably occur.

Despite these disadvantages, however, three reports have been published recently suggesting that corticotrophin has certain empirical advantages which make it the drug of choice for maintenance steroid therapy (West and Newns, 1955; Jordal, 1956; Savage, 1956a, b). All these authorities agree in insisting that for satisfactory and scientific control of corticotrophin therapy it is essential to have facilities for the routine estimation of the 17-hydroxycorticosteroid excretion in the urine. If, however, manufacturers can find a reliable method of standardizing the potency of their preparations biochemical control might well become superfluous.

HYDROCORTISONE

Hydrocortisone (free alcohol) is about 50 per cent. more potent than cortisone acetate (Boland, 1952b, 1955a), but the incidence of undesirable side-effects is no less. In the experience of one of us (J. H. G.) there are occasional patients who respond better to the naturally occurring hormone. Furthermore, there are occasional patients, detected only by trial and error, who seem to be more or less resistant to cortisone but obtain substantial relief from hydrocortisone, though this point is of less practical importance since the advent of the delta derivatives.

Hydrocortisone is also prepared in a solution suitable for intravenous administration (Hart, 1955).

CORTISONE DERIVATIVES

The discovery of the pharmacological actions of cortisone in 1949 led to intensive research directed towards discovering effective, safer, and cheaper analogues, and Hench and Ward (1954) list no fewer than sixty preparations which had been subjected to careful clinical trial. Mason and Polley (1950) concluded by a process of elimination that in order to possess anti-inflammatory properties the steroid nucleus must have certain characteristics, and seven years later their criteria have not been challenged. Effective modifications to the steroid nucleus have recently been achieved, and so far the correlation between laboratory data and clinical experience has been excellent, though only a limited number of substances have been subjected to sufficiently long clinical trials.

The Halogen Derivatives

These have little application in physical medicine. Some have about ten to twenty-five times the antirheumatic effect of cortisone and up to three times that of prednisone, but sodium and chloride retention and potassium loss are so marked that routine clinical use is precluded (Fried and Sabo, 1953, 1954; Thorn *et al.*, 1954; Goldfein *et al.*, 1955; Hart, 1956; Ward *et al.*, 1954; Boland and Headly, 1954; Villa *et al.*, 1956).

Aldosterone

This derivative has no immediate clinical application in the musculoskeletal diseases. It appears to be identical with the sodium-retaining corticoid present in human urine and originally named electrocortin (Simpson *et al.*, 1952). Ward *et al.* (1954) conclude that it has no detectable antiphlogistic effects.

Prednisone and Prednisolone*

Herzog *et al.* (1955) synthesized analogues of cortisone and hydrocortisone which differed from their parent substances only in the possession of a double bond in the 1–2 position of the "A" ring of the steroid nucleus, and which were found to be approximately three to four times as powerful as the original steroid when measured experimentally in animals. Bunim, Pechet, and Bollet (1955) administered these preparations to seven patients with rheumatoid arthritis, controlling their results with comprehensive metabolic studies, and confirmed that the new products were three to four times more potent as anti-inflammatory agents than cortisone.

Kinsell *et al.* (1955), in the light of experience in their series of cases, summarize the advantages and disadvantages of prednisone as compared with the other corticoids. Among the advantages they found were less sodium retention and potassium loss; no greater, and possibly less, calcium and phosphorus loss; significantly less tendency to produce mental aberration; and fewer "cushingoid" manifestations. Among the disadvantages were noted more gastric and intestinal complications (and hence the need for prophylactic anti-ulcer therapy); and probably a greater tendency to ecchymosis, the mechanism of which is not well understood.

As the result of clinical trials, reports greeting the new substances with varying degrees of enthusiasm have been published by Boland (1956), Hart *et al.* (1955), and De Sèze *et al.* (1956).

In this country an encouraging preliminary report has recently appeared of a multi-centre controlled trial carried out by the Medical Research Council and the Nuffield Foundation (Medical Research Council, 1957b) in which a comparison was made between the relative effectiveness of prednisone and cortisone in the treatment of rheumatoid arthritis in 68 patients, 35 of whom, selected at random, were changed from cortisone to prednisone. At the end of a year the cortisone group showed no material change. The prednisone group showed improvement in several respects, and in five cases the disease was judged to be inactive, whereas this did not occur in any of the cortisone group. The incidence of side-effects, particularly "moon-face", was much higher in the prednisone group—a fact possibly related to a dosage which was relatively high compared with the dosage of cortisone which was used.

Fearnley (1957) reports marked clinical improvement as judged by change in functional capacity and the patient's own assessment in nearly 90 per cent. of cases of rheumatoid arthritis treated with prednisone.

Spies *et al.* (1955) infer that a synergism of potency may be obtained by

* Also known as delta-1-cortisone and delta-1-hydrocortisone, and previously as "metacortandracin" and "metacortandralone", respectively.

combining small doses of prednisone with salicylates, and this contention is reiterated by Szucs *et al.* (1956) and by Robecchi *et al.* (1956). Most of the combined preparations now available seem to contain in one tablet a dose of the steroid so small as to be probably innocuous and possibly inert. It is the present authors' opinion that they confuse the prescription of steroid therapy and are best avoided, since the dosage of either drug can be controlled more conveniently and with greater accuracy if the steroid and salicylate are given separately: this is also cheaper and allows a choice of preparations.

All authorities appear to agree that the delta derivatives have an anti-phlogistic potency approximately four to five times greater than that of cortisone and three to four times greater than that of hydrocortisone, and therefore their initial and maintenance dosage should be approximately in these ratios. From all practical points of view prednisone appears to be identical to prednisolone when given systemically (Boland, 1955b).

Despite their lower dosage requirements the delta compounds are still significantly more expensive than their parent substances, but nevertheless they are rapidly becoming the drugs of choice in maintenance steroid therapy. There frequently appears to be an intangible but, to the patient, very real subjective improvement when a change is made from cortisone to prednisone or prednisolone (cf. Hart *et al.*, 1955).

The relative absence of sodium and therefore of fluid retention and potassium excretion is an advantage with these drugs upon which all authorities seem agreed. Possibly as a corollary of the diminished sodium retention, the risks of inducing hypertension also appear to be diminished. However, Nabarro *et al.* (1955) point out that the absence of electrolyte changes is virtually the only metabolic disturbance in which the delta derivatives are superior to cortisone, all other side-effects being found in approximately the same number of cases with equivalent dosages.

The problem of peptic ulceration in patients receiving steroid therapy has excited renewed interest with the introduction of the delta derivatives. Bollet *et al.* (1955) have found the reported incidence of peptic ulcer in a total of 477 patients treated with cortisone and corticotrophin to be 7·5 per cent. This figure must be evaluated against the background of a recorded incidence of 4·5 per cent. in 650 patients with rheumatoid arthritis who had never received hormone treatment (Bauer, 1952) and 6 to 8 per cent. as reported by Ragan (1952). Many experiences are quoted of patients whose proven duodenal ulcers were not reactivated or aggravated by cortisone, and a review of cases in which peptic ulcers have actually healed during steroid therapy has been published by Sandweiss (1954). In Bollet's series there was no apparent relationship between the duration of treatment or total dose of the drug and the appearance of the

ulcer. However, it is noted that radiological evidence of healing occurred within three weeks of the institution of conventional medical anti-ulcer therapy even when the dose of steroid was unreduced. This suggests that prophylactic measures might be taken with advantage in all cases treated with these drugs. Unfortunately, an ulcer may make its initial appearance in the form of a massive gastro-intestinal haemorrhage or by perforation with resulting peritonitis in the absence of warning symptoms.

The *Proceedings of the American Rheumatism Association* (American Rheumatism Association, 1955a, b) contains the views of several American authorities about these new drugs in the light of their accumulated experiences, and as a balanced symposium it is strongly recommended. The following points are abstracted from it. Calkins *et al.* (1955) found that both prednisone and prednisolone caused considerably larger losses of nitrogen and phosphorus than cortisone, whereas the excretion of calcium was approximately the same for both groups of drugs. (The relative daily doses in this experiment were 75 mg. of prednisone and 300 mg. of cortisone.) Slocumb confirmed that osteoporosis can be caused by prednisone to the same extent as by cortisone, this leading to a higher incidence of fractures than would normally be expected in rheumatoid arthritis: thus it was a good idea to combine these drugs with testosterone. Boland stated that it was necessary neither to restrict the sodium or fluid intake of a patient on prednisone nor to give added potassium salts or other diuretic agents. The delta compounds have proved equally effective in other collagen diseases, such as systemic lupus erythematosus, scleroderma, and polyarteritis nodosa, in which the relative potencies are the same as in rheumatoid arthritis (Steinberg and Roodenburg, 1956).

THE PROBLEM OF "CORTISONE RESISTANCE"

There is no doubt that a definite proportion of patients on maintenance steroid therapy appear to "escape" from adequate control after an excellent initial response and for no discernible reason. Many of these cases remain unsatisfactory thereafter on any safe dosage level. If the physician injudiciously raises the dose he is liable to exchange the symptoms of rheumatoid arthritis for those of hypercortisonism, to the possible confusion of the doctor and the certain unhappiness of the patient. Slocumb's (1952) conception of hypercortisonism as a cause of apparent worsening is interesting, but, despite the many contrasting features he lists, the differentiation of this syndrome from true rheumatoid "flare" is seldom easy. The correct treatment of this syndrome is a very gradual reduction in dosage.

There have been various reports about the "petering out" effect with prednisone, and the literature abounds in accounts of the same phenomenon

with cortisone: for example, Howell and Ragan (1956), discussing "induced hyperadrenalism", noted no fewer than seven well-authenticated references to it. It appears that the delayed "escape" from a satisfactory and constant maintenance dose is by far the most important single cause of "failed steroid therapy". Many mechanisms have been cited as possible aetiological factors (Hench and Ward, 1954; Wolfson *et al.*, 1950; Goslings *et al.*, 1951), but it seems indisputable that in the majority of these cases there is no satisfactory explanation within the limits of our knowledge. For these it seems justifiable to retain "cortisone resistance" or "tissue adaptation" as purely descriptive terms in the hope of stimulating further investigation in the laboratory. One possible clue exists, since there is some evidence that the phenomenon may be disease-specific; for example, while it appears to be well recognized in the "collagen" group of diseases and also in chronic asthma, it does not seem to occur to the same extent in chronic dermatological cases or in the treatment of sarcoidosis.

ADMINISTRATION AND DOSAGE

After eight years' experience there is still considerable controversy as to the best methods of administration and dosage regimens for maintenance therapy. Hench and Ward (1954) review no fewer than eleven schedules which have been advocated by different authorities. Although they regard four of these as being obsolete and two others as becoming so, they are worthy of careful study, partly for their historical interest but also because, having regard to the idiosyncrasies of both the patient and his disease, it is impossible to lay down a uniform programme for every case.

In endeavouring to represent current opinion it will be a help to consider the various points under two headings, depending on whether they are generally accepted or still controversial, and for the sake of simplicity we shall refer only to cortisone except where other derivatives are specifically indicated.

A. Generally Accepted Principles

The early fashion of starting with a very high dosage (e.g. 300 mg. per day) and rapidly reducing to a reasonable maintenance dose is to be strongly condemned even in desperate cases. It causes undue euphoria and makes it extremely difficult to arrive at a satisfactory maintenance dose with the patient's co-operation.

Men and children (assessed on a *pro rata* basis) on the whole tolerate the drug better than women and can usually be maintained safely on significantly higher dosage. Menopausal and post-menopausal women tolerate the drug worse than any other group, and obesity lowers the chance of a satisfactory tolerance in all groups. There is also some unconfirmed experimental evidence,

based on 17-hydroxycorticosteroid studies, that elderly patients need smaller doses to produce the same clinical effects than the young or middle-aged (Tyler *et al.*, 1955). In general, it is true to say that the more active the disease the higher will be the required dose.

In chronic disease intermittent therapy has little to recommend it except for certain short-term and specified objectives, such as to "cover" a manipulation. Therefore before steroid therapy is started the patient should be fully investigated, and the physician should be prepared to maintain the treatment over as long a period as proves necessary. Little is to be gained from alternating cortisone with ACTH as was formerly common (Kinsell *et al.*, 1955).

These drugs should never be administered less frequently that eight-hourly, and many patients do better with regular six-hourly administration. Variations in dosage, especially reductions, should be made as gradually as possible, and for this purpose the 5-mg. tablets of cortisone and 1-mg. tablets of the delta derivatives are very useful. Likewise very gratifying degrees of improvement can often be obtained by raising the maintenance dose by no more than 12·5 mg. of cortisone or 3 mg. of prednisone per day. The reason for this dosage sensitivity is obscure, but it almost seems as if the tissues attune themselves accurately to a certain range of variation in the circulating steroids, and any excursion outside the limits of this range is either resented or approved until the tissue "thermostat" can be adjusted to the new level. It must be remembered that the suprarenals will almost certainly be functionally inhibited if the maintenance treatment has been in progress more than a few weeks, and consequently their usual homoeostatic functions will not be operative.

Intercurrent illness, surgical operations, and other stresses are *never* indications for the precipitate withdrawal of steroid therapy, and this is especially important if the treatment has been in progress for more than a week or two. Indeed, a period of medical, surgical, or psychological "stress" is usually an indication for temporarily raising the dosage rather than lowering it, since the body will not be able to respond as it normally does by increasing corticosteroid secretion. It is therefore a common practice to give any patient receiving maintenance steroid therapy a "bonus" of approximately 200 mg. cortisone at 48, 24, and 2 hours before an operation. A dose of 100–200 mg. is generally given the next day, and then the dosage is gradually reduced to its pre-operative maintenance level (Slocumb and Lundy, 1952; Salassa, Bennett, *et al.*, 1953; Salassa, Keating, and Sprague, 1953). For emergency surgery, when oral therapy would be too slow-acting, it is a common practice to administer 200 mg. cortisone intramuscularly as soon as possible and again immediately before or after the operation, and in addition 100–200 mg. of soluble hydrocortisone should be given intravenously during the operation and

repeated as need be (Ward *et al.*, 1953). Many variations on this basic pattern have been successfully tried, and each incident must be assessed as a separate problem, especially in regard to the speed of withdrawal of the "bonus" dose.

Despite every precaution, however, a small proportion of patients will develop signs of adrenal failure when subjected to stress, and intravenous preparations of soluble hydrocortisone are an essential stand-by to deal with these emergencies. Similar precautions must also be taken with patients who are no longer taking cortisone but who have been on maintenance doses during the preceding six months, provided that these were of sufficient duration and magnitude to cause adrenal suppression. It may take the suprarenals as long as six or even twelve months to recover their normal response to stress, and perplexing and even fatal adrenal failure has been reported in cases with relatively minor stresses where the surgeon and anaesthetist were unaware of the potential risks (Salassa, Bennett, *et al.*, 1953; Salassa, Keating, and Sprague, 1953). The original theoretical objections to performing surgical operations on patients receiving cortisone for fear of the inhibition of wound healing are now known to have no clinical relevance in the dosages which are normally employed. A few surgeons, however, state that they leave their sutures in a few days longer than is their custom out of deference to the hypothetical risks.

It now seems generally agreed that the object of steroid therapy is not to render the patient symptom-free, except in those rare cases in which there is undue susceptibility to a dose which is within the safety limit. Instead, the aim is to find in each case a maintenance dose which will cause a worthwhile degree of symptomatic and functional improvement without risking side-effects which may be more unpleasant than the original symptoms.

Efforts to discover a synergist to cortisone which would potentiate its effects without increasing the risk of side-effects have so far failed. Insulin (Henderson *et al.*, 1950), *para*-aminobenzoic acid (Wiesel *et al.*, 1951), and glycyrrhetinic acid (Hart and Leonard, 1954) are among the substances that have been tested.

B. Controversial Principles

Before the end of 1953 the maintenance dose recommended in most authoritative publications ranged between 50 and 75 mg. of cortisone per day. Since 1953 the Mayo Clinic group of workers have considerably modified their dosage schemes in an effort to abolish the serious effects of hypercortisonism.

Polley's recommendations

In 1956 Polley, surveying these trends, made three suggestions: "Use of the smallest possible dose of the hormone at the start of, as well as during,

treatment is advised." "Most patients with rheumatoid arthritis should anticipate that sooner or later the inflammatory manifestations of their disease can be controlled adequately without supplemental hormonal treatment." Finally: "For post-menopausal women 20 to 30 mg. of cortisone or 3·5 to 5 mg. of prednisone daily is usually maximal. For pre-menopausal women the upper limit has been in the range of 30 to 37·5 mg. of cortisone or 5 to 6·5 mg. of prednisone daily. For adult men, 37·5 to 50 mg. of cortisone or 6 to 9 mg. of prednisone may be maximal if hypercortisonism is to be avoided."

It seems that, if interpreted literally, the first point, as to the use of the smallest possible dose at the start of as well as during treatment, may not be uniformly applicable. It is impossible to assess for individual patients what daily dosage they will require to make them comfortable, and it is much easier to manage a patient and to form a rapid assessment of the chances of successful maintenance therapy if the initial dose is sufficiently high to cause unequivocal objective improvement. The dose can then be rapidly diminished until a safe maintenance level is reached. If the initial high dosage does not result in sufficient objective improvement to warrant its continuation, there is no difficulty in withdrawing the drug completely within two or three days and the patient should suffer no permanent ill effects. By contrast, if the dosage is started at "the smallest possible dose" and then cautiously increased to a satisfactory maintenance level it is often difficult to reach the optimal dose within a matter of weeks. By this time the suprarenal glands will be functionally suppressed and, if it is decided that the patient's progress does not warrant further steroid therapy, the withdrawal may well prove tedious and unpleasant, and on occasions may result in a considerable flare in the disease.

The second point abstracted from Polley's article implies, if taken literally, that hormone therapy is usually to be regarded as a temporary phase of treatment until the disease becomes quiescent and can then be controlled with less powerful drugs. In practice, there is no doubt that this sequence of events does occur in many patients. However, it is quite impossible in the present state of our knowledge to predict in which case it will occur or, conversely, which patient will require life-long steroid maintenance therapy, and it therefore seems to be an unwise philosophy to adopt in case selection. It is safer, in our view, to select every patient on the assumption that he *may* require permanent therapy, to reject any who are constitutionally or psychologically unfitted for this, and then to rejoice in our good fortune each time it is possible to withdraw the drug because of a remission in symptoms. In this way fewer unsuitable patients will be selected for treatment simply out of a natural, but often misguided, desire to help them over a temporary flare.

Polley's third point concerns the maintenance dose levels which he regards

as satisfactory and desirable in the various groups of patients. It is probably true that the maximum dosages which he postulates are the maximum levels in each group compatible with the *complete* absence of hypercortisonism. But in our experience the limited degree of improvement which is obtained in most cases when using this low dosage justifies a somewhat bolder approach. In each case it is necessary to try to balance the inconvenience and possible dangers of hypercortisonism against the pain, ill-health, and functional disability caused by the arthritis. In general, it would seem that a mild degree of hypercortisonism is a justifiable price to pay if the advantage to the patient consists in increased functional autonomy or a significant improvement in general health. It is possible to attain this only if the patient is kept under careful observation so that the incidence of serious side-effects may be detected early and appropriate counter-measures taken at once.

MAYO CLINIC SCHEME

At the Mayo Clinic a significant reduction in dosage has been achieved by a scheme Hench has aptly named "dose tailoring", by which he means those refinements of daily and weekly dosages which he contends are not only logical, but essential to successful and safe therapy. Features of their regimen include the following principles:

(1) There should be no set dosages and no fixed periods between doses except in special cases.

(2) Dose reductions are started not after many days or a few weeks but promptly (often within four to seven days) after the first dose—that is, as soon as initial improvement is definite even though relief may be far from complete. Each new dose should be given a short test period, and if this is successful the next reduction should be made within a few days. In the early stages the decrements should not be more than 5–15 mg. of cortisone, and later as the total daily dose gets smaller the decrements should rarely be more than 2·5 or 5 mg. Reductions should continue so long as improvement is maintained.

(3) Premature increments of cortisone to deal with episodes of mild subjective deterioration are to be deprecated—extra aspirin, rest, or heat for one or two days may be enough. For a mild but definite flare an increment of 5 mg. may suffice; for a moderate flare the first increment should be 5–10 mg., depending on the patient's previous experience. As any flare *begins* to recede the daily dose should be reduced promptly but gradually. Intelligent patients soon learn how much extra cortisone they need for flares of different intensities.

(4) A "maintenance" dose is not the dose one "maintains" and it should not be a more or less fixed dose. "Maintenance" should refer rather to the degree of relief obtained than to the dosage of the drug used.

(5) Refinements in the total weekly dose can be achieved if one appreciates that most rheumatoid patients have, each week, about two good, three average, and two worse days. A patient frequently knows before noon what the rest of the day will be like. If he is comfortable throughout the week on a constant dosage he is taking enough for the worst two days and more than enough for the other days. This mild unrecognized overdosage may amount to 35–50 mg. per week, and its correction may make the difference between prolonged tolerance and the slow development of hypercortisonism. The patient should learn to regard his best day's dose as his regular dose to be supplemented by two or three small increments for other days as necessary.

(6) Refinements in the total *daily* dose can be made by utilizing the characteristic variation in severity of symptoms during the course of the day. To provide the smoothest effect advantage should be taken of these hours of improvement and the time and amount of each dose division made irregular in an appropriate manner. If there are no clinical variations the prescription should be distributed in four equal doses with an accurate six-hourly interval between doses. From such rearrangements of the total daily dose small but important dose reduction can be made in the course of a week.

These abstracts from the Mayo Clinic recommendations have been paraphrased essentially from three publications: Hench and Ward (1954), Ward *et al.* (1953), and Hench (1954). They illustrate a progressive and imaginative approach to the problem of maintenance therapy which may be held by some to err on the side of caution. Unfortunately, they necessitate not only considerable and intelligent co-operation from the patient, which is not always forthcoming, but also frequent and sometimes lengthy medical consultations. However, they are strongly commended as *principles* to guide our prescriptions, whether we use the low-dosage regimen recommended or the rather higher one which is customary in this country.

(To be concluded)

References

American Rheumatism Association (1955a) *Ann. rheum. Dis.*, **14**, 417.
——— (1955b) Ibid., **14**, 325.
Ansell, B. M., Bywaters, E. G. L., and Isdale, I. C. (1956) *Brit. med. J.*, **1**, 1075.

BAUER, W. (1952) *Proceedings of the Conference on the Effects of Cortisone*, p. 56. Merck and Co., Rahway, N.J.
——— and ROPES, M. W. (1956) *Practitioner*, **177**, 431.
BILKA, T. J., and WEIL, M. H. (1955) *Ann. intern. Med.*, **42**, 638.
BOLAND, E. W. (1952a) *J. Amer. med. Ass.*, **150**, 1281.
——— (1952b) *Brit. med. J.*, **1**, 1559.
——— (1955a) *Ann. rheum. Dis.*, **14**, 232.
——— (1955b) Ibid., **14**, 424.
——— (1956) *J. Amer. med. Ass.*, **160**, 613.
——— and HEADLY, N. E. (1954) *Ann. rheum. Dis.*, **13**, 291.
BOLLET, A. J., BLACK, R., and BUNIM, J. J. (1955) *J. Amer. med. Ass.*, **158**, 459.
BROCHNER-MORTENSEN, K., and FISCHER, F. (1953) *Acta med. scand.*, **145**, 97.
BUNIM, J. J., PECHET, M. M., and BOLLET, A. J. (1955) *J. Amer. med. Ass.*, **157**, 311.
——— ZIFF, M., and MCEWEN, C. (1955) *Amer. J. Med.*, **18**, 27.
CALKINS, E., REZNICK, L., and BAUER, W. (1955) *Ann. rheum. Dis.*, **14**, 419.
COPEMAN, W. S. C., DODDS, C., SAVAGE, O., GLYN, J. H., and FEARNLEY, M. E. (1954) *Brit. med. J.*, **1**, 1109.
DE SÈZE, S., DEBEYRE, N., and BORDIER, P. (1956) *Bull. Soc. méd. Hôp. Paris*, **72**, 216.
EHRENBERG, A. S. C. (1954) *Brit. med. J.*, **2**, 363.
EMPIRE RHEUMATISM COUNCIL (1955) *Ann. rheum. Dis.*, **14**, 353.
FEARNLEY, G. R. (1957) *Brit. med. J.*, **2**, 294.
FRIED, J., and SABO, F. F. (1953) *J. Amer. chem. Soc.*, **75**, 2273.
——— ——— (1954) Ibid., **76**, 1455.
GLYN, J. H. (1954) *Brit. med. J.*, **1**, 1376.
GOLDFEIN, A. L., LAIDLAW, J. C., HAYDAR, N. A., RENOLD, A. E., and THORN, G. W. (1955) *New Engl. J. Med.*, **252**, 415.
GOSLINGS, J., HIJMANS, W., QUERIDO, A., and KASSENAAR, A. A. H. (1951) *Brit. med. J.*, **2**, 698.
HANSEN, K. B., FISCHER, F., and BROCHNER-MORTENSEN, K. (1956) *Acta rheum. scand.*, **1**, 8.
HART, F. D. (1955) *Brit. med. J.*, **1**, 454.
——— (1956) Ibid., **2**, 940.
——— CLARK, C. J. M., and GOLDING, J. R. (1955) *Lancet*, **2**, 998.
——— and LEONARD, J. C. (1954) Ibid., **1**, 804.
——— ——— and CALEY, F. (1954) *Brit. med. J.*, **1**, 1205.
HENCH, P. S. (1952) *A.M.A. Arch. intern. Med.*, **36**, 1.
——— (1954) *Documenta Rheumatologica*, p. 19. J. R. Geigy, Ltd.
——— KENDALL, E. C., SLOCUMB, C. H., and POLLEY, H. F. (1949) *Proc. Mayo Clin.*, **24**, 181.
——— and WARD, L. E. (1954) *Medical Uses of Cortisone, including Hydrocortisone and Corticotrophin*, ed. F. D. W. Lukens. Blakiston Co., New York.
HENDERSON, E., GRAY, J. W., WEINBERG, M., and SENECA, H. (1950) *J. clin. Endocr.*, **10**, 800.
HERZOG, H. O., MOBILE, A., POLKSDORF, F., CHARMEY, W., HERSHBERG, E. D., PERLMAN, P. L., and PECHET, M. M. (1955) *Science*, **121**, 176.
HILL, A. B. (1954) *Brit. med. J.*, **1**, 1437.
HOWELL, D. S., and RAGAN, C. (1956) *Medicine (Baltimore)*, **35**, 83.
INGLE, D. J. (1950) *J. clin. Endocr.*, **10**, 1312.
JORDAL, R. (1956) *Dan. med. Bull.*, **3**, 24.
KINSELL, L. W. (1954) *Ann. rheum. Dis.*, **13**, 307.
——— MICHAELS, G., and FRISKEY, R. W. (1955) *First International Conference on the Clinical and Metabolic Effects of Meticorten and Meticortelone.*

Lancet (1956) Annotation, **2**, 666.
LANSBURY, J. H. (1956) *Amer. J. med. Sci.*, **231**, 616; **232**, 8, 12.
LOXTON, G. E. (1956) *Brit. med. J.*, **2**, 240.
MAINLAND, D. (1955) *Ann. rheum. Dis.*, **14**, 337.
MASON, H. L., and POLLEY, H. F. (1950) *J. Amer. med. Ass.*, **143**, 1474.
MEDICAL RESEARCH COUNCIL AND NUFFIELD FOUNDATION (1955) *Brit. med. J.*, **2**, 695.
——— ——— (1957a) Ibid., **1**, 847.
——— ——— (1957b) Ibid., **2**, 199.
NABARRO, J. D. N., WALKER, J. S., and WALKER, G. (1955) *Lancet*, **2**, 993.
POLLEY, H. F. (1956) *Brit. med. J.*, **2**, 1253.
RAGAN, C. (1952) *Proceedings of the Conference on the Effects of Cortisone*, p. 56. Merck and Co., Rahway, N.J.
ROBECCHI, A., DANEO, V., and MARRAZZI, G. (1956) *Reumatismo*, **8**, 121.
SALASSA, R. M., BENNETT, W. A., KEATING, F. R., and SPRAGUE, R. G. (1953) *J. Amer. med. Ass.*, **152**, 1509.
——— KEATING, F. R., and SPRAGUE, R. G. (1953) *Proc. Mayo Clin.*, **28**, 662.
SANDWEISS, D. J. (1954) *Gastroenterology*, **27**, 504.
SAVAGE, O. (1956a) *Lancet*, **2**, 926.
——— (1956b) *Ann. rheum. Dis.*, **15**, 410.
SIMPSON, S. A., TAIT, J. F., and BUSH, I. E. (1952) *Lancet*, **2**, 226.
SLOCUMB, C. H. (1952) *Bull. rheum. Dis.*, **3**, 21.
——— and LUNDY, T. S. (1952) *Surg. Clin. N. Amer.*, **32**, 1105.
SMART, G. A. (1956) *Brit. med. J.*, **1**, 1243; **2**, 239.
SOLEM, J. H., and RÖMKE, O. (1956) *Acta rheum. scand.*, **1**, 243.
SPIES, T. D., STONE, R. E., LOPEZ, G. G., TELLECHEA, C. M. D., TOCA, R. L., and REBOREDO, A. (1955) *J. Amer. med. Ass.*, **159**, 648.
SPRAGUE, R. G. (1951) *Amer. J. Med.*, **10**, 567.
STEINBERG, C. L., and ROODENBURG, A. I. (1956) *Ann. intern. Med.*, **44**, 316.
STEINBROCKER, O., TRAEGER, C. H., and BATTERMAN, R. C. (1949) *J. Amer. med. Ass.*, **140**, 659.
SWIFT, S. (1954) *Ann. Allergy*, **12**, 172.
SZUCS, M. M., HOLONKO, V., FORSTER, K. M., and NALAGAN, D. (1956) *Ohio St. med. J.*, **52**, 722.
THORN, G. W. (1954) Paper read before the Endocrine Society.
——— FORSHAM, P. H., FRAWLEY, T. F., RICHARDSON-HILLS, S, Jnr., ROCHE, M., STAEHELIN, D., and WILSON, D. L. (1950) *New Engl. J. Med.*, **242**, 783.
TOONE, E. G., and IRBY, R. (1955) *Amer. J. Med.*, **18**, 41.
TOUSSAINT, J. (1955) *Rev. Rhum.*, **22**, 205.
TYLER, F. H., EIK-NES, K., SANDBERG, A. A., FLORENTIN, A. A., and SAMUELS, L. T. (1955) *J. Amer. Geriat. Soc.*, **3**, 79.
VILLA, L., SALA, G., and BALLAVIO, C. B. (1956) *Ann. rheum. Dis.*, **15**, 237.
WARD, L. E., POLLEY, H. F., SLOCUMB, C. H., and HENCH, P. S. (1953) *J. Amer. med. Ass.*, **152**, 119.
——— ——— ——— ——— MASON, H. L., MATTOX, V. R., and POWER, N. H. (1954) *Proc. Mayo Clin.*, **29**, 649.
WEST, H. F. (1956) *Ann. rheum. Dis.*, **15**, 124.
——— and NEWNS, G. R. (1955) *Lancet*, **1**, 578.
WIESEL, L. L., BARRITT, A. S., and STUMPE, M. W. (1951) *Amer. J. med. Sci.*, **222**, 243.
WOLFSON, W. O., BEIERWALTES, W. H., ROBINSON, W. D., DUFF, I. F., JONES, J. R., NORPE, C. T., and EYAAB, M. (1950) *J. Lab. clin. Med.*, **36**, 1005.

ORIGINAL PAPER

SCORBUTIC RHEUMATISM

WITH REPORT OF A CASE

BY J. H. GLYN AND E. J. MORAN CAMPBELL

From the Departments of Physical Medicine and of Medicine, The Middlesex Hospital, London

THAT a patient with scurvy was recently referred to the physical medicine department as a case of osteoarthritis has prompted us briefly to review the relationship between ascorbic acid metabolism and "rheumatism". The subject can conveniently be considered under three main headings: (1) the mimicry of rheumatism by scurvy; (2) the relation of ascorbic acid to connective-tissue metabolism; and (3) the possible role of ascorbic-acid deficiency in rheumatoid arthritis.

SCURVY PRESENTING AS RHEUMATISM

In 1753 James Lind wrote: "Why the scurvy should so frequently and in so singular a manner affect the cartilages of the ribs . . . and why it seats itself so commonly in the joint of the knee, I am at a loss to account for." The association between the conditions and the diagnostic dilemma it presents seem to have been well established by 1860 when Fauvel published "Quelques remarques à propos d'un cas de scorbut aigu à forme rheumatismal".

The gross lesion which causes the severe pain is more commonly a periarticular periostitis than an intra-articular lesion (Comroe, 1953), but Morgan and Gault (1941) in their study of a large outbreak of scurvy noted that a significant proportion of their patients also developed haemarthrosis.

In 1953 Krebs, reporting the results of experimentally induced scurvy in 19 human volunteers, described one man who developed bilateral knee effusions and ecchymoses during the thirtieth week. In this experiment it was interesting to note that no detectable changes occurred until after the seventeenth week of deprivation. The first changes to be observed were enlargement and keratosis of the hair follicles—all except one of these cases eventually became haemorrhagic. The effusions did not occur until the thirtieth week.

ASCORBIC-ACID AND CONNECTIVE-TISSUE METABOLISM

Turning now from a purely clinical approach to survey some of the studies of the relationship between ascorbic-acid and connective-tissue metabolism, it would be appropriate to start with two quotations. The first is from Follis (1951): "It would seem best to designate scurvy as that part of the over-all

picture of ascorbic-acid deficiency which is characterized by a failure of certain specialized cells—i.e., fibroblasts, osteoblasts, and odontoblasts—to promote the deposition of their respective fibrous proteins—collagen, osteoid, and dentine." The second quotation is from Wolbach and Howe (1926), who characterized the condition of scorbutus as "inability of the supporting tissues to produce and maintain intercellular substances".

It therefore appears that a lack of vitamin C affects the metabolism of osteoblasts and that this fundamental disturbance is followed by morphological changes as a result of mechanical forces.

Follis (1951) has done much detailed work on scorbutic guinea-pigs. He found that there was a reduction in cytochrome oxidase activity in rib-tissue slices; there was also a complete absence of phosphatase activity, which can be restored by small doses of ascorbic acid. No reduction in the glycogen content of the hypertrophic cartilage cells was observed, at least not until inanition reached a very advanced stage. By contrast, the mucopolysaccharides of the osteoid tissue were found to lose their metachromatic staining properties, but this returned with the administration of ascorbic acid. Curiously enough, Follis states that this loss of metachromatic staining does not apply to cartilage whose mucopolysaccharides retain a positive reaction with the periodic-acid–Schiff reagent even in an animal dying of scurvy.

This apparent sparing of the cartilage is surprising, since in 1952 Wolbach and Maddock obtained strong evidence that cartilage is affected in scurvy in common with all the other supporting tissues. Indeed, cartilage is a very favourable tissue for the study of the sequences of scurvy and its repair. The rapidly growing young guinea-pig's cells cease to form matrix and assume appearances quite unlike the normal: the cells become shrunken and irregular with densely staining nuclei.

The final abnormality described by Follis was the disappearance of ribose nucleic acid from the osteoblasts and young osteocytes, this again being reversible by treatment with ascorbic acid.

Our understanding of the pathogenesis of scurvy is in turn dependent on an understanding of the normal mechanisms operating in the formation of fibrous protein of the connective-tissue group. Of these processes we know very little. However, in 1941 Hunt described the reversion of newly formed collagen to an argyrophil precancellous state, and Pirani and Levenson (1953) also found that adequate intake of ascorbic acid was necessary for the maintenance of scar tissue which has formed in healed wounds over a period of many weeks. There is a rapidly increasing volume of research concerned with various aspects of collagen metabolism which, it may be hoped, will ultimately elucidate, amongst other phenomena, the true relationship between collagen and ascorbic acid.

Finally, with regard to muscles, it has long been known that degeneration of striated muscle is common in scurvy. Hyaline degeneration and fragmentation of the fibres with great proliferation of nuclei are usually described. Boyle and Irving (1951) found that the myofibrils pulled back at their periosteal attachments, leaving a normal sarcolemmal sheath.

ASCORBIC-ACID METABOLISM AND RHEUMATOID ARTHRITIS

McCormick (1955) believes that ascorbic-acid deficiency is the cause of rheumatoid arthritis. Much of this author's conviction seems to be based on the experimental work of Rinehart *et al.* (1934), who found that prolonged inadequacy of vitamin C in the diet produced functional impairment and anatomical changes in the joints and that these were accentuated if infection was superimposed. Their conception was that latent scurvy rendered the subject a susceptible host, and if infection supervened rheumatic fever was likely to result. In 1935 Rinehart extended this concept to include rheumatoid arthritis. Similar views have been expressed by Mouriquand (1951).

For a clinical refutation of these concepts of a simple relationship between rheumatism and ascorbic-acid depletion one need look no farther back than 1950, when after the announcement of the discovery of the effects of cortisone on rheumatoid tissues there was a widespread fashion of treating rheumatoid arthritis by the intramuscular injection of 5 mg. deoxycortone acetate followed five minutes later by the intravenous injection of 1 g. of ascorbic acid (Lewin and Wassen, 1950). Like so many new treatments, this regimen produced some dramatic results in the early days, especially in the hands of its protagonists. However, the ultimate results were disappointing. Finally a letter to the medical press signed by a group of rheumatologists from the Empire Rheumatism Council (Copeman *et al.*, 1950) decrying the practice resulted in its virtual abandonment. There are still some, however, who believe that the occasional startling results obtained suggest that there may be some obscure relationship between ascorbic-acid metabolism and rheumatoid arthritis. Few florid cases of scurvy are now seen in this country, and it may seem fanciful to attribute any disease as common as rheumatism to this cause. There are, it is true, many well-authenticated references to a deficiency of this vitamin in established disease (Race, 1937; Stone, 1947; Abbasy and Harris, 1937), but this has generally been considered to be a *post hoc* phenomenon. However, McCormick (1954) regards this as a superficial interpretation. He states that during his fifteen years' practice as a nutritionist more than 5,000 qualitative tests for vitamin-C status have been made in a variety of general medical conditions, and

less than 10 per cent. of adult subjects have been found to be at what he considers the optimal level in this respect. Infants and children fare better because of the almost routine inclusion of citrus and other fresh fruit juices in their diet.

CONCLUSION

This short review is not intended to argue that there is a simple relationship between ascorbic-acid depletion and any form of rheumatic disease. Indeed, as pointed out, clinical evidence strongly opposes such a view. However, in dealing with musculo-skeletal disorders it is important that we should learn as much as possible of the experimental and basic scientific approaches to anomalies of the connective tissue in order to follow current trends of thought, coordinate them, and seize on their possible clinical implications at as early a stage as possible. We have purposely avoided introducing another fascinating link between connective-tissue disorders and ascorbic-acid metabolism—namely, its metabolism by the adrenal cortex and the effect of stress and of corticotrophin on its release into the plasma. Limitations of space preclude an adequate discussion of these important topics, but the reader is referred to papers by McSwiney *et al.* (1954) and by Abelson and Baron (1952) for an introduction to the subject.

Details of the case referred to in our opening paragraph are appended.

CASE REPORT

A married woman, aged 64, originally attended the hospital in August, 1956, complaining of a rash on both legs. This rash, which was not irritating, had appeared regularly during the past three or four summers. She mentioned quite incidentally that for the preceding three or four weeks she had suffered a little pain in both knees, the left being considerably worse than the right. She attributed all her symptoms to a fall on the knee eight months previously. The knees were X-rayed, and since the films showed considerable osteoarthritis with loose-body formation the patient was given a supply of liniment and was transferred for physiotherapy.

History

In 1930 the patient had been treated for a duodenal ulcer in another hospital by orthodox medical and dietetic methods: her symptoms soon disappeared. There was no other history of relevant illness, accident, or operation. Her mother and father died when the patient was young. Three siblings and two sons were all well. There was no history of familial haemorrhagic disease.

The patient lived with her husband and one of her sons. They were not poverty-stricken. The patient was responsible for cooking an evening meal, which usually consisted of meat and two vegetables. Initially she strongly denied that she did not eat a full diet herself, although she admitted that she was seldom hungry. Because vitamin-C deficiency seemed possible she was questioned further about her diet. She then admitted that because of the pain she had suffered from her duodenal ulcer in

1930 she had been frightened of eating a normal diet, and had later developed anorexia so that she no longer felt the need for a full mixed diet. In fact, for the past thirty years, with minor variation, her diet had been as follows: 5 a.m., cup of tea with sugar; 9 a.m., cup of beef extract with biscuits; no midday meal at all; 5 p.m., cups of tea and bread-and-butter (4 slices) with paste. Occasionally she had a banana, a slice of corned beef, or an egg. She ate nothing between 5 p.m. and retiring to bed. She ate no more than two or three oranges a year, and no other fruit. She never had green vegetables or potatoes, and frequently went for a whole day without food.

She weighed 6 stones 5 lb. and thought that she had got markedly thinner in the past two years. She had noted no tendency to bruising or excessive bleeding. In fact, apart from tiredness and a mild winter cough, she asserted that she was in excellent health and was only troubled by her presenting symptoms.

Physical Examination

The patient was a thin, short, grey-haired woman who looked considerably older than her years. She had some mild koilonychia, and two loose tooth stumps in her lower jaw surrounded by haemorrhagic, swollen and tender gums. She was otherwise edentulous and did not wear any artificial teeth. Apart from the region of the stumps, the remainder of her gums looked healthy. There was a patchy haemorrhagic rash below the knees. She also had a large ecchymosis over the right external malleolus. Her left knee was swollen and extremely tender and brawny. There was also an overlying ecchymosis spreading round to the thigh. The joint was hot and any movement was very painful. The right knee showed evidence of chronic osteoarthritis only.

Full examination of her cardiovascular, respiratory, alimentary, and central nervous systems revealed no other abnormalities. There were no enlarged lymph nodes and the spleen was not palpable.

On clinical grounds a diagnosis of haemarthrosis of the left knee possibly due to scurvy was made. The differential diagnoses considered at this stage were: arthritis associated with leukaemia, an obscure haemorrhagic disease, and carcinomatosis.

Laboratory Investigations

These revealed the following: Hb 58 per cent. R.B.C. 3,100,000 per c.mm. Colour index 0·9; P.C.V. 27 per cent.; M.C.V. 90 cu.μ; M.C.H.C. 31 per cent.; W.B.C. 8,900 per c.mm. (51 per cent. neutrophils, 40 per cent. lymphocytes, 8 per cent. monocytes, 1 per cent. eosinophils). Bleeding time 3 minutes; clot retraction normal; coagulation and prothrombin concentration normal. Platelets 480,000 per c.mm. Hess's test strongly positive. Blood urea 35 mg. per 100 ml. Plasma proteins 6·6 g. per 100 ml. (albumin 3·7 g., globulin 2·9 g.). Plasma ascorbic acid 0·15 mg. per 100 ml. (normal 1–1·5 mg.).

X-ray examination of her knees, as already mentioned, showed marked osteoarthritic changes with loose-body formation. Dental radiographs revealed considerable alveolar recession and some retained roots.

Treatment

At the time of her admission she was excreting 2 mg. of ascorbic acid in eight hours, but when put on the normal ward diet this figure rose to 6·5 mg. in eight hours.

She was then given 700 mg. of ascorbic acid each morning and the ascorbic acid excretion measured. On the first day of this regimen she excreted only 3·6 mg. in the eight-hour period, and on the second day only 2·5 mg. By the seventh dose of 700 mg. she was still excreting only 19·4 mg. in eight hours, but on the eighth day she excreted 120 mg., and then in subsequent days 70 mg., 120 mg., and 110 mg. Any eight-hour excretion test in which less than 10 per cent. of the loading dose is excreted in the first eight hours is considered to indicate ascorbic-acid depletion, therefore these saturation tests suggested that the patient was grossly depleted of this vitamin.

Apart from these large doses of ascorbic acid the only medication the patient received in hospital was ferrous sulphate tablets, 6 gr. thrice daily.

By the end of treatment her plasma ascorbic acid level had risen to 1·2 mg. per 100 ml., and a bone-marrow examination during treatment showed a marked erythroid hyperplasia with a myeloid hypoplasia.

Clinical Progress

The improvement in her clinical condition was very dramatic. The pain and swelling in the knee subsided rapidly until only a very small effusion and no pain remained. There was a full range of movement, and the purpuric rash both around the knee and in the rest of the leg disappeared completely, leaving behind only a slight discoloration. The tooth stumps were removed and the gums returned to normal. Her appetite improved and she gained 5 lb. in weight. Following a short period of convalescence she appeared to be perfectly well and returned to her normal household duties. On routine follow-up in the out-patients department six months later she was completely fit.

SUMMARY

Some of the apparent relationships between ascorbic-acid metabolism and rheumatic disease are briefly reviewed, inspired by a typical case of scurvy which had been referred to the department of physical medicine as a case of osteoarthritis of the knees. There appears to be no simple relationship between ascorbic-acid depletion and any form of rheumatic disease; indeed, clinical evidence strongly opposes such a view.

The clinical history and laboratory findings in the case in point are given in detail. Large doses of ascorbic acid led to dramatic improvement in the patient's clinical condition, the joint pain and swelling subsiding rapidly and the plasma ascorbic acid level returning to normal.

Acknowledgment

We are grateful to Professor A. Kekwick and Dr. A. C. Boyle for permission to publish this case.

References

Abbasy, M. A., Harris, L. J., and Ellman, P. (1937) *Lancet*, **2**, 181.
Abelson, D., and Baron, D. N. (1952) Ibid., **2**, 663.
Boyle, P. E., and Irving, J. T. (1951) *Science*, **114**, 372.

COMROE, B. I. (1953) *Arthritis and Allied Conditions*, ed. J. L. Hollander *et al.*, p. 872. Lea and Febiger, Philadelphia.
COPEMAN, W. S. C., and others (1950) *Lancet*, **1**, 830.
FAUVEL, A. (1860) *Gaz. méd. Orient*, **8**, 127.
FOLLIS, R. H. (1951) *Bull. Johns Hopk. Hosp.*, **89**, 9.
HUNT, A. N. (1941) *Brit. J. Surg.*, **28**, 436.
KREBS, H. A. (1953) *Proc. Nutr. Soc.*, **12**, 237.
LEWIN, E., and WASSEN, E. (1950) *Acta med. scand.* Suppl., **246**, 99.
LIND, J. (1753) *A Treatise of the Scurvy*. Sands, Murray, and Cochran, Edinburgh.
MCCORMICK, W. J. (1954) *Arch. Pediat.*, **71**, 29.
—— (1955) Ibid., **72**, 107.
MCSWINEY, R. R., CLAYTON, B. E., and PRUNTY, F. T. G. (1954) *Lancet*, **1**, 179.
MORGAN, J., and GAULT, A. S. (1941) *Chinese med. J.*, **60**, 141.
MOURIQUAND, G. (1951) *Presse méd.*, **59**, 71, 1473.
PIRANI, C. L., and LEVENSON, S. M. (1953) *Proc. Soc. exp. Biol.* (*N.Y.*), **82**, 95.
RACE, J. (1937) *Rep. chron. rheum. Dis.*, **3**, 30.
RINEHART, J. F. (1935) *Ann. intern. Med.*, **9**, 671.
—— CONNOR, C. L., and METTIER, S. R. (1934) *J. exp. Med.*, **59**, 97.
STONE, K. (1947) *Diseases of the Joints and Rheumatism*. Grune and Stratton, New York.
WOLBACH, S. B., and HOWE, P. R. (1926) *Arch. Path. Lab. Med.*, **1**, 1.
—— and MADDOCK, C. L. (1952) *A.M.A. Arch. Path.*, **53**, 54.

ORIGINAL PAPER

THE EFFECT OF COOLING ON MUSCLE EXCITABILITY

By DAVID M. ZAUSMER

*From the Department of Studies in Psychological Medicine, University of Liverpool**

THE following investigation arose out of a pilot study of the muscle excitability of child tiqueurs. It was found that the wide variations of rheobase and chronaxie made comparisons between individual tiqueurs and between tiqueurs and normal subjects meaningless. In order to reduce experimental errors and environmental fluctuations to a minimum a rigidly standardized technique for the measurement of excitability was devised, based on the experience of other investigators. The reliability of the method was checked in a small group of normal subjects by serial recordings of intensity–duration (I/T) curves under controlled conditions. The sensitivity of the instrument in detecting small changes in excitability was determined by lowering the skin temperature, which is a variable known to influence excitability (Harris, 1952).

The selection of a suitable index of excitability was discussed with Dr. A. T. Richardson, and he suggested using a multiple of the rheobase because of its convenience and because it avoided the need to locate the motor point. (The advantages of rheobase ratios for recording I/T curves have been discussed elsewhere (Bauwens, 1952).) As a result the numerical index adopted was the ratio between the minimal voltage required to produce a contraction at 0·01 msec. pulse-length and the rheobase.

APPARATUS

A Ritchie–Sneath constant-voltage muscle stimulator (Walter and Ritchie, 1945) with 10 pulse lengths ranging from 300 to 0·01 msec. was used. The repetition rate was set at one pulse per second. The stimulating electrode was constructed of a silver disk (diameter 1 cm.) attached to a screw set in a "perspex" clamp and covered with lint soaked in electrode jelly. The indifferent electrode was a sheet of zinc wrapped in eight layers of lint and soaked in 2 per cent. saline.

The abductor pollicis brevis was selected for stimulation because the contraction of the muscle belly was easily visible and the clamp could be conveniently attached to the thenar eminence.

* Present address: Crayford Child Guidance Clinic, Barnehurst, Kent.

METHOD

Thirteen university students took part in the investigation, and were tested on an average of ten occasions in the same room maintained at a fairly constant temperature. The subjects remained in the room for fifteen to thirty minutes before being tested, and the apparatus was switched on during this period.

(*a*) The skin of the forearm and thenar eminence was cleansed thoroughly with ether-meths, electrode jelly was rubbed over the site of stimulation, and the stimulating electrode was firmly clamped over the centre point of the abductor pollicis brevis. The indifferent electrode was bandaged to the forearm and the subject's hand was placed comfortably in supination on a table under a bright light.

Starting at 300 msec. pulse length, the intensity of the pulses was increased until a muscle twitch was just visible. A period of half to one minute was allowed to elapse, during which the contractions became more marked and a lowering of voltage was required to reach the threshold again. These adjustments were repeated until the threshold voltage remained constant. The end-point was defined as the voltage at which a contraction was just visible and which remained constant when the threshold was obtained either from above or below that value. (The contraction almost invariably disappeared when the threshold was lowered by one volt.)

The pulse durations were then decreased from 300 msec. to 0·01 msec. and the ten threshold values were recorded. It was found that the end-point remained constant from 300 to 3 msec. and then increased with each successive decrease in pulse length. The rise in threshold when plotted on a log–log graph was rectilinear, as described by Richardson (1952).

(*b*) The experiment was repeated with the electrodes on the opposite arm.

(*c*) The clamp was removed and the subject's hand was immersed in cold running water for one minute. The skin was dried, electrode jelly was reapplied, and the clamp replaced. The skin temperature at the thenar eminence was recorded with a Light Laboratories skin thermometer before and after stimulation.

(*d*) The same procedure was repeated with the opposite hand.

(During these experiments the fluctuations in mains voltage were recorded. The variations were negligible and were certainly insufficient to have affected the results.)

RESULTS

The findings are presented in the table overleaf. It will be seen that there was an increase in excitability index (that is, a decrease in muscle excitability) with cooling in 12 of the 13 subjects.

EFFECT OF COOLING ON EXCITABILITY INDEX AS MEASURED BY STIMULATION OF ABDUCTOR POLLICIS BREVIS

Subject	Warm		Cool		Difference between Means
	Mean	Range	Mean	Range	
1	1·64	1·4–2·0	1·93	1·7–2·1	+0·29
2	2·28	2·0–2·6	2·48	1·9–2·8	+0·20
3	1·91	1·4–2·5	1·99	1·6–2·7	+0·08
4	1·84	1·5–2·3	2·25	1·7–2·6	+0·41
5	2·05	1·6–2·8	2·12	1·6–2·6	+0·07
6	1·55	1·2–1·9	1·84	1·7–2·0	+0·29
7	2·09	1·8–2·4	2·20	1·9–2·8	+0·11
8	2·10	2·0–2·3	2·50	2·3–2·6	+0·40
9	1·60	1·6–1·6	2·20	2·2–2·2	+0·60
10	2·35	2·3–2·4	2·40	2·3–2·5	+0·05
11	2·01	1·8–2·3	2·06	1·9–2·3	+0·05
12	1·80	1·6–2·0	2·00	2·0–2·0	+0·20
13	1·55	1·4–1·8	1·53	1·3–1·7	−0·02

The room temperature throughout the investigation was $22·8° \pm 1·7°$ C.; the change of temperature at each session was $1·0° \pm 0·8°$ C.

The skin temperature at room heat was $27·1° \pm 1·4°$ C. and the temperature of the water $9·0° \pm 1·6°$ C. The skin temperature after cooling the hands for one minute and before stimulation was $22·1° \pm 1·4°$ C., and immediately after stimulation was $24·8° \pm 2·6°$ C. The rise in temperature was $2·7° \pm 1·6°$ C., and the interval of time between the two temperature recordings $5·9 \pm 1·9$ minutes.

The differences between the excitability indices of the right and left hands at room temperature and after cooling were not statistically significant.

The differences between the indices at room temperature and on cooling in individual cases were significant at the 5 per cent. level in three subjects only (Nos. 4, 6, 8). However, the differences between the paired indices of the whole group were highly significant ($t = 3·750$, $p < 0·001$).

The rheobase alone was found to be unreliable as a measure of excitability, because the individual variations were considerable and there was no consistent hange in the rheobase with cooling.

SUMMARY

The muscle excitability of thirteen normal subjects was studied. A Ritchie-Sneath constant-voltage stimulator was used to stimulate the abductor pollicis brevis, and the index of excitability adopted was a multiple of the rheobase.

The effect on the excitability index of cooling the hands was also investigated. A statistically significant reduction in excitability was demonstrated with a fall in skin temperature of between 5·0° and 2·3° C. Individual results were unreliable in spite of the standardized technique employed.

Acknowledgments

I wish to thank Dr. S. Barton Hall for making this investigation possible, Dr. A. T. Richardson for technical advice, Dr. R. Harris for his constructive criticism, and the students of the Department of Psychology who acted as subjects.

References

Bauwens, P. (1952) In *The Diagnosis of Nervous Diseases*, by J. Purves-Stewart and C. Worster-Drought, 10th ed., p. 769. Arnold, London.

Harris, R. (1952) *Ann. phys. Med.*, **1**, 126.

Richardson, A. T. (1952) Ibid., **1**, 88.

Walter, W. G., and Ritchie, A. E. (1945) *Electron. Engng*, **17**, 585.

REVIEWS OF BOOKS

CLINICAL ORTHOPAEDICS, NO. 8—Chronic Hereditary Diseases and Developmental Anomalies. Editor-in-Chief: Anthony F. DePalma. With the assistance of the Associate Editors, the Board of Advisory Editors, and the Board of Corresponding Editors. *Pp. 337. Single volumes 60s.; subscription price 48s. Philadelphia and Montreal: J. B. Lippincott Company. 1956.*

The introduction to this book states that "*Clinical Orthopaedics* is designed for the publication of original articles offering significant contributions to the advancement of surgical knowledge". The title suggests that the book is a comprehensive review of the subject mentioned, but unfortunately it falls short of this objective.

The first section does indeed deal with subject-matter related to the title, and the standard of individual contributions is high. One chapter outlines present knowledge on the genetics of joint diseases, and the conclusions reached, especially in relation to rheumatoid arthritis, are of considerable interest. A section on the problem of heredity in diseases of the hip is also included. Other chapters cover a wide range of subjects, including: environmental causes of abnormal embryonic development; spondylolisthesis; congenital dislocation of the hip; Milroy's disease; osteogenesis imperfecta; and heredity as a factor in malignancy.

"Splinting for Controlled Movement", by Mr. Denis Browne, is one of the longest chapters and is a lucid exposition of his views on this subject. Another chapter is devoted to a study of the extraordinarily high incidence of lumbar neural arch defects in Alaskan natives—Eskimos and Aleuts—"a figure that ranges from 15 to 50 per cent. according to the geographic area".

The second section, headed "General Orthopaedics", opens with an admirable study of haemophilic arthropathy. The next eleven chapters, however, are more in the nature of random jottings on a variety of subjects, and many of these contributions scarcely merit their place in a work of this standard. It is difficult to justify the inclusion of a chapter on the scapulo-costal syndrome, which makes an unimpressive debut as a clinical entity, or on "Carpometacarpal Dislocation—A Case Report". There is a useful contribution on problems related to prosthesis in childhood, but the contributions on "The Physician's Fee", "The Physician in Relation to Corporations", and "The Expert Medical Witness" are of mainly academic interest to British readers.

The third section forms an incongruous postscript. It is headed "Motorist Injuries and Motorist Safety" and is claimed to be a symposium written primarily for clinicians. However, it will be of practical use only for those who are fortunate enough to be employed in an advisory capacity to motor-car manufacturers. The advice is no doubt sound, but one would scarcely expect to find it in a work dealing with hereditary and developmental diseases.

Having briefly indicated the contents of this book, it remains to be said that its value is somewhat diminished by its omissions. If the editorial board had included contributions outlining modern views on all conditions of interest in orthopaedics having a hereditary or developmental aetiology the book would have been of increased value. Thus it seems a pity that no space was found for contributions on such subjects as achondroplasia, diaphysial aclasis, osteopetrosis, dyschondroplasia, or Morquio's disease. The list could be continued, but enough has been said to indicate that this

book is not as comprehensive as the title might suggest. The first section is well written and is worthy of detailed study, but much extraneous matter might have been omitted with advantage in the other two sections. R. W. BARTER

RHEUMATIC DISEASES, RHEUMATISM AND ARTHRITIS. By Heinrich G. Brugsch, M.D., F.A.C.P. *Pp. xlv + 330; illustrated. 80s. Philadelphia and Montreal: J. B. Lippincott Company. London: Pitman Medical Publishing Co. Ltd. 1957.*

This book has been written for the senior student or the younger postgraduate student, and serves as an introduction to the study of those painful disorders of the locomotor system which fall within the clinical sphere of the physician practising physical medicine.

The text is succinct, lucid, and readable, and gives essentially practical rather than theoretical detail. In format the volume closely resembles the larger textbooks on the subject, with the usual rather tiresome chapter on statistics followed by anatomical and physiological considerations, laboratory procedures, X-ray diagnosis, and therapeutic measures. It is refreshing to find on reading the chapter on physical therapy that the limitations of this form of treatment, together with the principles of its prescription, are so well understood by a general physician.

The clinical chapters describe acute rheumatism and the four major chronic arthritides, and a chapter is also devoted to the collagen diseases. The chapter on soft-tissue lesions is perhaps not up to the general standard of the rest of the book, but this may well be due to some confusion because of a differing nomenclature in this country. For instance, it is doubtful if British physicians would accept a diagnosis of pleurodynia in the presence of a pleural effusion.

These defects are, however, few, and for those who wish for a short account of the subject of the rheumatic diseases this book is excellent, and the bibliography at the end of each chapter may serve as an introduction to wider reading.

A. C. BOYLE

THE PRINCIPLES AND PRACTICE OF DIATHERMY. By B. O. Scott. *Pp. 193. 25s. London: Heinemann. 1957.*

This book is written for "students of short-wave therapy" and succeeds in packing a good deal of useful information into relatively few pages. The subject is dealt with very thoroughly from fundamentals to refinements. The first half of the book deals mainly with the physics, and the second half with the effects and application, of short-wave diathermy. The penultimate chapter consists of a well-illustrated and detailed guide to regional application of short waves. At the end of each chapter a bibliography is given for further reading.

By the very nature of the book it is not easily readable, but it repays careful study and is so arranged that it proves easy for reference, although there is a little unnecessary duplication. It is particularly pleasing to note that the author has avoided the long list of conditions that can be treated by short-wave diathermy, so beloved by the older textbooks on this subject. In the chapter on dosage the author suggests that

in prescribing short-wave therapy the doctor should indicate to the physiotherapist the diagnosis, the part to be treated, and also the technique to be used, including details of intensity, frequency, and duration. I disagree that in the average case the technique to be used should be prescribed. If the diagnosis, the part to be treated, and the objective of treatment are stated, then the technique to achieve that objective should be left to the physiotherapist, who has been trained in the correct application of short-wave diathermy. In a later chapter the author does make amends when he states that "in general, however, details of the technique will be left to the physiotherapist".

The book is neatly produced on good paper with clear printing and plentiful illustrations. I feel sure that it will become the vade mecum on this subject for all physiotherapists; a copy should certainly be obtained for every physiotherapy department, and especially for those concerned with undergraduate or postgraduate teaching. For the specialist in physical medicine it should be a useful reference volume, and to the aspiring specialist an aid in preparing for the first part of the Diploma.

A. ZINOVIEFF

PROCEEDINGS OF THE SECOND INTERNATIONAL CONGRESS OF PHYSICAL THERAPY, NEW YORK, 1956. *Pp. 208. 22s. 6d. New York: American Physical Therapy Association. London: Chartered Society of Physiotherapy. 1957.*

The editors of these *Proceedings* have been faced with the problem that is common to all editors of the records of international congresses: from the nature of their task they are forced to include all the scientific papers read at the Congress. Many of the papers would have been improved by editing and shortening, and from a scientific point of view some of them could have been left out without detriment to the account of the Congress. I should have liked to have seen the panel discussion and symposium kept separate from the scientific papers. The criticism of the arrangement of the subject-matter is that reports on the business of the Congress tend to occur amongst the scientific papers; and again, the scientific papers tend to be mixed, so that a paper on manual muscle testing appears many pages after papers on exercise therapy.

The panel discussion on poliomyelitis and the symposium on prosthetics make excellent reading and are of great value to students and qualified physiotherapists alike. Certain of the scientific papers do not come up to this high standard, particularly the paper on "Research by Physical Therapists in Electromyography", in which an account is given of the work of Mr. Chester Pike. His work would not receive credit from any experienced worker in this field, and many would regard his submissions as monstrous.

From my reading of the *Proceedings* it is obvious that there is a great shortage of suitably qualified physiotherapists throughout the world, and speakers from all nations make a plea for an increased number in their ranks. It is extremely gratifying to note the very high regard the Chartered Society of Physiotherapy has in this international field. Physicians in physical medicine and physiotherapists should read this account of the Second International Congress, so that they may have a deeper understanding of their common problem.

D. WILSON

ABSTRACTS OF THE LITERATURE

Ankylosing Spondylitis. H. J. GIBSON. *J. Fac. Radiol.* (*Lond.*), 1957, **8**, 193.

This is a useful review of the aetiology and pathology of ankylosing spondylitis. Whilst this disease and rheumatoid arthritis are similar in many ways, they are not identical. In ankylosing spondylitis inflammation, at any rate in the spinal joints, is minimal and bony ankylosis common, although in the peripheral joints similar changes are seen in both diseases. Rose's differential agglutination test is negative in ankylosing spondylitis, even when there is peripheral joint involvement. S. MATTINGLY

Ankylosing Spondylitis. B. A. STOLL. *J. Fac. Radiol* (*Lond.*), 1957, **8**, 201.

The author believes that radiotherapy may be of value in ankylosing spondylitis because the adrenal glands are stimulated by irradiation. A small number of cases were therefore treated by irradiation of the adrenals with apparent improvement. If this was confirmed in a large group of cases a much lower dose of radiation could be used in the treatment of this disease with greater safety.

S. MATTINGLY

Polyradiculitis (Landry–Guillain–Barré Syndrome): Treatment with Cortisone and Corticotrophin. P. H. JACKSON, H. MILLER, and K. SCHAPIRA. *Brit. med. J.*, 1957, **1**, 480.

The authors review the literature on this syndrome and describe five cases seen by them over the last three years. These new cases and others reported in the literature have been treated with cortisone or corticotrophin. The results are regarded as encouraging, though improvement is unpredictable and inconstant.

D. A. BREWERTON

Stenosing Tenosynovitis of the Common Peroneal Tendon Sheath. R. W. PARVIN and L. T. FORD. *J. Bone Jt Surg.*, 1956, **38A**, 1352.

The authors describe a condition in the peroneus longus identical to de Quervain's disease. The lesion is clinically in all respects the same, and is relieved by partial or total excision of the thickened tendon sheath.

C. B. WYNN PARRY

Spontaneous Rupture of the Extensor Tendons in the Hand Associated with Rheumatoid Arthritis. L. R. STRAUB and E. H. WILSON. *J. Bone Jt Surg.*, 1956, **38A**, 1208.

Spontaneous rupture of the extensor tendons in the hands of five patients with chronic rheumatoid arthritis was found to be associated with subluxation of the distal end of the ulna at the inferior radio-ulnar joint. Three cases were treated successfully by tendon repair and excision of the distal end of the ulna. Spontaneous rupture of these tendons is probably not rare in rheumatoid arthritis, but is often overlooked because of the severity of other deformities in these patients. S. MATTINGLY

The Plastic Replacement of Severed Flexor Tendons of the Fingers. T. L. SARKIN. *Brit. J. Surg.*, 1956, **44**, 232.

The difficulties of treatment of lesions of the flexor tendons in the finger are well known. The accepted treatment to-day is grafting of the profundus tendon and usually excision of the sublimis. The author points out that this technique requires highly skilled surgery and post-operative rehabilitation.

In view of the long time involved, a new technique is described where the

tendon is replaced by a double length of strong nylon covered by polythene tubing passing through the tendon sheath. Preliminary results are encouraging; post-operative rehabilitation is very much shortened, and patients have regained full movements and power in the finger.

C. B. WYNN PARRY

Joint Contractures. T. H. HOWELL. *Proc. roy. Soc. Med.*, 1957, **50**, 70.

The author classifies joint contractures found in the chronic sick as follows: (1) Postural contractures the consequence of maintaining a flexed position in bed, response to treatment depending mainly on the mental attitude of the patient. (2) Contractures due to disease of the central nervous system, most frequently found associated with hemiplegia. Surgical measures have a limited place in the management of neurogenic contractures. (3) Contractures due to chronic arthritis: these are the outcome of a vicious circle of joint pain, muscle spasm and immobility in flexion, and progress from reflex muscle spasm to fibrosis, then ankylosis.

Ultrasonic radiations were found to be of particular value in the second stage of contracture, and an investigation of its use is described.

P. J. R. NICHOLS

Joint Contractures in Children. D. BROWNE. *Proc. roy. Soc. Med.*, 1957, **50**, 69.

Joint contractures in children are classified as follows:

(1) *Congenital contractures.*—(*a*) Intrinsic—(i) normal limitation of movement, a transient phenomenon; (ii) due to abnormal pressures *in utero* resulting in failure of muscular development and periarticular fibrosis, these responding badly to manipulation and immobilization. (*b*) Extrinsic—due to malposition *in utero* and including "idiopathic scoliosis".

(2) *Acquired contractures.*—The most important of these are due to the muscle imbalance of cerebral palsy or following poliomyelitis.

The author strongly emphasizes the importance of correct splintage for the equinus deformity of cerebral palsy.

P. J. R. NICHOLS

Still's Disease. Clinical and Pathological Features. The Use of Reconstructive Surgery. M. E. SCALA and C. SILVER. *Bull. Hosp. Jt Dis.*, 1956, **17**, 211.

A discussion of Still's disease and its pathology and radiological features is presented. Surgical procedures available at different stages of the disease, with indications, contraindications, and associated problems, are reviewed.

The surgical rehabilitation of a female with crippling Still's disease is described. This involved arthroplasty procedures on both elbows and hips, osteotomy of the lower legs, and multiple operations on the hands. A plea is made for massive surgical planning in such cases.

D. C. ARNOTT

Reticulohistiocytosis (Lipoid Dermatoarthritis). R. P. WARIN, C. D. EVANS, M. HEWITT, A. L. TAYLOR, C. H. G. PRICE, and J. H. MIDDLEMISS. *Brit. med. J.*, 1957, **1**, 1387.

This paper describes four patients with a similar and unusual syndrome of a widespread papular and nodular skin eruption and polyarthritis. Tendon-sheath swellings and patches of xanthelasma palpebrarum occurred in two cases. Histological examination of all involved tissues in every case revealed the presence of giant cells containing lipoid material. Radiographs showed changes resembling

those of rheumatoid arthritis, though bone destruction was marked. Two patients died, and, apart from widespread infiltration of tissues by giant cells, fibrinous pericarditis was present. Twelve cases showing a similar clinical picture and histology, described in the literature under a variety of names, are reviewed. S. MATTINGLY

Calcification of Articular Cartilage. H. BUNJÉ and W. R. COLE. *J. Bone Jt Surg.*, 1956, **38B**, 874.

The authors describe a case of polyarthritis with calcification of articular cartilage. The patient, a young woman, suffered from short-lived attacks of fever and acute joint pain. She did not admit to past venereal disease, but was thought to have had gonorrhoea. Gout and rheumatoid arthritis were suspected, but the authors concluded that the cause of the arthropathy was unknown, and that the deposition of calcium in the peripheral layers of hyaline cartilage was secondary to joint inflammation.

S. MATTINGLY

Chronic Sporotrichal Synovitis of the Knee. F. S. WEBSTER and D. WILLANDER. *J. Bone Jt Surg.*, 1957, **39A**, 207.

Infection with *Sporotrichum schenkii* has rarely been reported as a cause of bone or joint disease. The authors describe a case of monarticular arthritis affecting the knee due to infection with this fungus which presented insidiously in a farmer aged 30 and was confirmed by cultures of blood and joint fluid. The infection proved resistant to large doses of potassium iodide and stilbamidine, both drugs producing toxic effects. Treatment by excision of the granulomatous synovial membrane and arthrodesis of the joint was apparently successful, though the period of follow-up was short.

S. MATTINGLY

The Response to Injury of Rat Synovial Membrane. A. LEVENE. *J. Path. Bact.*, 1957, **73**, 87.

The changes in synovial membrane following relatively slight trauma have been studied experimentally in the rat, the knee-joint being opened and a small piece of synovium excised.

It was found that in twenty-four hours a fibrin mass fills the gap; acute inflammatory reaction occurs in the surrounding tissue. On the second day the exudate contains polymorphonuclear leucocytes and fibrin; the adjoining uninjured synovial cells are unchanged and no mitoses occur. Healing occurs by granulation tissue, and a new surface layer of fibroblasts round off to resemble the adjacent synovial cells. By twenty-one days scar tissue is inactive and the regenerated synovium has no distinguishing features. The uninjured synovial cells, being inert, have played no part in the repair process.

MAURICE F. HART

A Pathological Review of Degenerative Shoulder Lesions. J. S. NEVIASER and S. H. EISENBERG. *Bull. Hosp. Jt Dis.*, 1956, **16**, 297.

The authors set out to clarify the aetiology of the painful shoulder by means of gross and microscopic pathological specimens taken at operation and at necropsy.

In infancy the shoulder capsule is separated from the associated tendons by loose areolar tissue; in the adult it is most difficult to demonstrate a line of demarcation. This is probably a significant factor in degenerative shoulder pathology.

The macroscopic and microscopic appearances of calcific tendinitis, adhesive capsulitis, subdeltoid bursitis, and bicipital tendinitis are described and discussed. D. C. ARNOTT

Surgery of the Periarthritides of the Shoulder. M. J. MICHOTTE. *Brit. J. phys. Med.*, 1957, **20**, 77.

Degenerative and traumatic lesions of the musculo-tendinous cuff, lesions of the tendon of the long head of biceps and of the coraco-humeral ligament, and lesions of the synovial membrane of the shoulder-joint and of its extensions are described. The diagnosis and differential diagnosis of these conditions are discussed, and details of the medical and surgical treatment advocated in the author's practice given.

The place of arthrography in the diagnosis of rupture of the musculotendinous cuff is clarified. The interesting observation is made that with a powerful deltoid in association with a minor tear operation is always necessary, whereas with a weak deltoid, even when there is a major tear, restoration of function by re-education and without operation is much more likely. The diagnosis of a lesion of the long head of biceps is detailed, and the use of arthrography to differentiate the stiffness due to this cause from the true "frozen shoulder" is shown.

When medical and physical measures fail in all the lesions discussed the author is confident that a successful surgical solution can be found.

D. C. ARNOTT

Intermittent Hydrarthrosis. S. MATTINGLY. *Brit. med. J.*, 1957, **1**, 139.

Intermittent hydrarthrosis is characterized by periodic joint effusions, usually affecting one or both knee-joints. The cause is not known. Some patients develop rheumatoid arthritis. Spontaneous remissions and relapses are common and make assessment of prognosis and treatment difficult.

Three cases are described; in two, remissions were apparently induced by chrysotherapy and radiotherapy.

Intermittent hydrarthrosis may be an unusual variant of rheumatoid arthritis, but permanent joint damage is not inevitable. It could, however, be a syndrome accompanying various joint disorders, the periodicity of the effusions being related to normal but exaggerated cyclical changes in the tissues of the patient. Treatment is, of necessity, empirical and usually ineffective; radiotherapy, chrysotherapy, and synovectomy may induce at least a temporary remission. *Author's Summary*

Rheumatoid Arthritis of Larynx. J. E. G. PEARSON. *Brit. med. J.*, 1957, **1**, 1047.

Rheumatoid Arthritis of the Crico-arytenoid Joints. W. S. C. COPEMAN. *Brit. med. J.*, 1957, **1**, 1398.

Laryngeal Stridor in Rheumatoid Arthritis due to Crico-arytenoid Joint Involvement. O. A. BAKER and E. G. L. BYWATERS. *Brit. med. J.*, 1957, **1**, 1400.

These three papers describe involvement of the crico-arytenoid joints in rheumatoid arthritis presenting with hoarseness and laryngeal stridor. Severe attacks of dyspnoea may occur and death may result from laryngeal obstruction. Delta-cortisone may be of value in treating acute attacks, though cortisone may aggravate the condition, possibly because of its salt-retaining properties.

S. MATTINGLY

Agranulocytosis due to Phenylbutazone. F. L. JAMES and R. E. GEESAMAN. *Ann. intern. Med.*, 1957, **46**, 152.

The authors report a case of agranulocytosis in a patient treated for a cervical disk lesion with 400 mg. phenylbutazone daily for a period of five weeks. The illness presented with a diffuse macular rash and sore throat. The patient recovered following treatment with cortisone, penicillin, and streptomycin, though bone-marrow function was not restored

for eleven days after phenylbutazone was discontinued. It is suggested that this delay may have been due to slow excretion of the drug.

S. MATTINGLY

The Effect of Phenylbutazone and a Related Analogue (G25671) upon Thyroid Function. J. A. LINSK, B. C. PATON, M. PERSKY, M. ISAACS, and H. S. KUPPERMAN. *J. clin. Endocr.*, 1957, **17**, 416.

This is the report of a study to confirm the previous findings in man on the effect of phenylbutazone upon the uptake of radioactive iodine by the thyroid and to correlate this effect with the attained plasma level of phenylbutazone. An analogue of phenylbutazone—namely, 4-(phenylthioethyl)-1 : 2-diphenyl-3 : 5-pyrazolidinedione, or G25671—was also tested.

Thirteen euthyroid patients were used for study. Phenylbutazone was administered orally in a daily dose of 800 mg. for four days. ^{131}I was given on the fourth day. A consistent and marked reduction in thyroidal uptake of ^{131}I occurred in every case. In four patients G25671 was tested, and this caused no depression in ^{131}I uptake. When phenylbutazone was continued for more than four days the inhibiting action on thyroidal ^{131}I uptake wore off.

It is suggested that phenylbutazone induces a temporary or partial suppression of thyroid-stimulating hormone action. MAURICE F. HART

The Effect of Salicylates and Adrenocortical Hormones on C-reactive Protein. A. J. LEWIS, E. PADER, and S. K. ELSTER. *Amer. J. med. Sci.*, 1957, **233**, 309.

C-reactive protein appears as an acute phase response in a variety of abnormal conditions. In rheumatic fever C-reactive protein is found, but disappears under treatment with salicylates or adrenocortical hormones, or both. It is uncertain whether these drugs cause the disappearance of C-reactive protein by a non-specific effect upon the protein or by suppression of the inflammatory processes that produce it.

To determine this point a study has been made of patients with carcinoma and C-reactive protein. It was found that the level of C-reactive protein was not reduced after the administration of acetylsalicylic acid, cortisone, prednisone, and adrenocorticotrophin gel. It is therefore concluded that these drugs have no direct effect on the metabolism of C-reactive protein. In acute rheumatic fever the disappearance of C-reactive protein is probably due to the suppression of the inflammatory process.

MAURICE F. HART

Deaths Associated with Steroid Hormone Therapy. K. D. ALLANBY. *Lancet*, 1957, **1**, 1104.

From 1949 to 1955 more than 400 patients at Guy's Hospital were treated with cortisone or corticotrophin. The author reviews the case histories of 18 patients who died during treatment, excluding patients who were receiving substitution therapy for Addison's disease or hypopituitarism, or after adrenalectomy and hypophysectomy for malignant disease. Infection was the commonest cause of death (seven cases), but three patients died from gastro-intestinal haemorrhage and three from gastro-intestinal perforation. Steroid therapy was considered directly responsible for eleven deaths and probably hastened death in three further cases.

The author concludes that adrenal failure is a serious risk if additional stress such as infection occurs in patients treated with steroids, and in these circumstances dosage must be increased rather than reduced. Regular and careful

observation of patients treated with these hormones is essential.

S. MATTINGLY

Diagnosis, Treatment and Prevention of Chronic Hypercortisonism in Patients with Rheumatoid Arthritis. C. H. SLOCUMB, H. F. POLLEY, L. E. WARD, and P. S. HENCH. *Ann. intern. Med.*, 1957, **46**, 86.

Hypercortisonism is described as a condition which occurs when excessive doses of cortisone, related adrenocortical hormones, or ACTH are administered. The acute type of hypercortisonism occurs when large doses are administered in acute diseases, resulting in increase in weight, fluid retention, facial rounding ("moon-face"), irregular menses, acne, and hypertrichosis. Chronic hypercortisonism follows prolonged overdosage with steroids, often when such overdosage is mild or unsuspected, developing over weeks or months in the long-term treatment of chronic diseases.

Patients vary widely in their tolerance to steroid therapy, post-menopausal women being the most susceptible. Chronic hypercortisonism is characterized by cyclic swings of mood and other symptoms, such as increased fatigue, muscle and joint pains, alternating with periods of well-being. It must be distinguished from relapses of the disease; synovitis is minimal, however, and pains are not relieved by physiotherapy or aspirin. In a minority of patients more severe reactions occur. Of 128 patients with symptoms of chronic hypercortisonism seen at the Mayo Clinic between 1951 and 1954, 18 developed disseminated lupus erythematosus and 5 polyarthritis nodosa.

The authors advise a gradual reduction of dosage of steroids in patients presenting with chronic hypercortisonism. Doses of cortisone may have to be reduced by as little as 2·5 or 5 mg. every three to seven days, the total daily dose being divided and equal doses given every six to eight hours. Frequent adjustments of dosage are often necessary. Other measures include long periods of rest, salicylates (2–4 g. daily), and additional vitamins.

It is suggested that chronic hypercortisonism may be avoided by keeping the dose of steroids low in the treatment of chronic diseases. For maintenance a daily dose of cortisone of less than 10 mg. in children, 10–35 mg. in women, and 35–50 mg. in men is advised.

[This paper should be read by all who prescribe steroid therapy for patients with rheumatoid arthritis.]

S. MATTINGLY

Comparison of Cortisone and Prednisone in Treatment of Rheumatoid Arthritis. Report by the Medical Research Council and Nuffield Foundation. *Brit. med. J.*, 1957, **2**, 199.

The object of the investigation reported was to determine whether patients suffering from rheumatoid arthritis who had been taking cortisone acetate for a year or more would benefit by a change of treatment to prednisone acetate. Of the 68 patients who entered the trial 35, chosen at random, were transferred to prednisone therapy, while the remainder continued to take cortisone. The dose of prednisone initially was one-third that of the cortisone the patient was receiving on entry, but was subsequently adjusted to the individual patient to obtain maximum benefit without side-effects. Both groups were followed for a year.

The patients on cortisone showed, on average, no significant change for better or worse. Patients on prednisone, however, showed improvement as measured by strength of grip, erythrocyte sedimentation rate, general functional capacity, and disease activity, and five patients were judged to be in remission at the end

of a year. The benefit was most marked in the first three months.

In both groups radiographs of hands and feet showed an increase in bone erosions in about one-third of patients. Two patients on cortisone died, one from a perforated duodenal ulcer and the other from subarachnoid haemorrhage; a further patient developed a duodenal ulcer. One patient on prednisone died from "asphyxia", and was found to have honeycomb lungs at post-mortem examination. Two patients on prednisone developed gastric ulcers, and two further patients developed a sudden and unexplained fall in haemoglobin level.

The incidence of side-effects, especially "moon-face", was higher in the prednisone group, and, in view of this, the more favourable results observed with prednisone may be due, in part, to the use of a dose which was relatively high when compared with that of cortisone.

S. MATTINGLY

Results of Radiotherapy in Osteoarthritis of the Hip. A. G. H. MURLEY. *Lancet*, 1957, **1**, 818.

Less than one-quarter of 57 patients with osteoarthritis of the hip derived subjective benefit from irradiation of the hip-joint. In only five patients did benefit last longer than a year.

S. MATTINGLY

Psoriasis and Arthritis. V. WRIGHT. *Ann. rheum. Dis.*, 1956, **15**, 348.

Of 42 cases of psoriasis and arthritis studied, 34 had an "erosive arthritis", 6 degenerative joint disease, 1 gout, and 1 rheumatic fever. The author concluded that 32 of the 34 patients with psoriasis and an "erosive" arthritis were suffering from a disease which was distinct from rheumatoid arthritis. This disease was milder and remissions were frequent, males being affected as often as females; joint stiffness was a common complaint, and in one-third of the cases acute attacks of joint pain resembling gout were recorded. Three patients had ankylosing spondylitis. Involvement of the small joints of the hand and feet was common; when the terminal interphalangeal joints were affected psoriasis of the nails was already present or developed later. Rose's differential agglutination test was negative in these 32 cases, but positive in two further cases of "erosive" arthritis, thought to be rheumatoid arthritis on clinical grounds.

S. MATTINGLY

Psoriasis and Arthritis: Study of Radiographic Appearances. V. WRIGHT. *Brit. J. Radiol.*, 1957, **30**, 113.

The radiographs from 39 patients with psoriasis and arthritis were studied. Six patients had degenerative arthritis and one gout, and the radiographs were typical for these conditions. The radiographs from 32 patients with psoriasis and "erosive arthritis" were compared with those of patients with uncomplicated rheumatoid arthritis. Similar changes were observed in both groups, and whilst the earliest changes seen radiologically in psoriatic patients were marginal erosions at the edges of the articular surface, they were by no means pathognomonic of the condition. These erosions appeared most commonly in the distal interphalangeal joints, and the base of the phalanx was sometimes expanded, giving the appearance of an inverted golf tee. The tip of the terminal phalanx was sometimes eroded and appeared to have been whittled down to a point, and this change was not seen in patients with rheumatoid arthritis. The involvement of terminal phalanges and distal interphalangeal joints was sometimes related to involvement of the nails.

There was a relatively high incidence of clinical ankylosing spondylitis in the

patients with psoriasis and erosive arthritis (3 out of 32), and an even higher incidence of changes seen radiologically in the sacro-iliac joints.

S. MATTINGLY

The Clinical Entity of Anterior Crural Ischaemia. L. BLUM. *Arch. Surg. (Chicago)*, 1957, **74**, 59.

This short paper describes four cases of a condition, better known in this country as the anterior tibial syndrome, caused by sudden arterial occlusion. It is concluded that the lesion is not one of infarction alone, contributory factors being the narrowness of the osteofascial space and lack of collateral blood supply.

C. B. WYNN PARRY

Recovery and Rehabilitation following Coronary Occlusion. A. M. MASTER, H. L. JAFFE, and R. W. KISSANE. *Dis. Chest*, 1956, **30**, 593.

In this paper, which forms part of a symposium on rehabilitation in cardiovascular disease, the authors conclude that at least four out of five patients following coronary occlusion make a satisfactory or complete functional recovery and are able to perform useful work for many years.

D. C. ARNOTT

A Muscle-tendon Transposition for Paralysis of the Lateral Abdominal Muscles in Poliomyelitis. J. M. CLARK and A. AXER. *J. Bone Jt Surg.*, 1956, **38B**, 475.

This paper describes the transposition of the tensor fasciae latae and the iliotibial band as active muscle transplants to replace paralysed lateral abdominal muscles in poliomyelitis. The transplant is swung up and inserted into the ninth rib through a subcutaneous tunnel. This improves thoraco-pelvic stability and the balance of asymmetrically paralysed abdominal muscles.

C. B. WYNN PARRY

Tendon Transference in Poliomyelitis. A. MÖLLERUD. *Acta orthop. scand.*, 1956, **26**, 222.

Commonly accepted prerequisites of successful tendon transfer are reviewed; among them are stressed: (*a*) that fixed deformity must be corrected, and there must be some free passive movement in the joint which is to be moved by the transferred muscle; (*b*) that full power must be present pre-operatively in the muscle whose tendon is to be transferred.

Indications for (*a*) operating on children and (*b*) operating on the foot without stabilizing procedures are discussed, the advantage of placing the transferred tendon subcutaneously being stressed. A series of 185 tendon transfer operations performed during a ten-year period are followed up and analysed.

D. C. ARNOTT

Discussion on an Evaluation of the Methods of Increasing Muscle Strength. D. A. BREWERTON. *Proc. roy. Soc. Med.*, 1956, **49**, 1006.

The author carried out a number of experiments to determine whether it mattered where in the joint range maximum resistance was applied in an exercise. An apparatus was devised in which resistance could be applied at any point in the range of knee flexion. The force of extension was measured in different positions in 100 normal and 400 abnormal conditions.

Two conclusions were reached: (1) when the quadriceps is weak in one position it is proportionately weak throughout the range; (2) it is immaterial in what position maximum resistance is applied. The presence of a painful joint has, however, a profound effect on the choice of type of exercise and the position at which resistance is applied. In general, the position chosen should be that where the pain is least, and if pain is severe the exercise should be static.

Finally the author discusses the importance of a functional approach to exercise, the training of skill, and motivation.

C. B. WYNN PARRY

Traction Therapy: A Study of Resistance Forces. B. JODOVICH and G. R. NOBEL. *Amer. J. Surg.*, 1957, **93**, 108.

A new traction bed is described in which the resistance of the lower body is eliminated as it is transported mechanically—intermittent traction being given by a motor. Good clinical results are claimed, but this is only a preliminary report—no controls are presented and the interest of the paper lies in the apparatus.

C. B. WYNN PARRY

Physical Measures in the Aged. D. L. ROSE and W. S. ALYEA. *J. Amer. med. Ass.*, 1956, **162**, 1524.

Two physical aspects of disability in the aged have been especially studied—namely, the inefficiency of respiration and the inadequacy of ambulation. Habitual under-ventilation of the lungs was suspected in some patients because their vital capacity increased so promptly and so greatly after a programme of breathing exercises and because this was accompanied by so marked an improvement in general condition and attitude. Similar evidence led to the conviction that the early achievement of ambulation in the elderly patient is more important than the concentrated exercising of particular groups of weakened muscles.

Authors' Summary

The Problem of the Aged Amputee. M. WARREN. *Postgrad. med. J.*, 1957, **33**, 436.

This is an excellent account of the problem that is well worth reading in the original.

D. A. BREWERTON

Effect of Physiotherapy on Post-operative Pulmonary Complications. O. WIKLANDER and U. NORLIN. *Acta chir. scand.*, 1957, **112**, 246.

Pulmonary complications following upper abdominal operations were studied in 200 patients. Half of these patients were treated with "breathing exercises" and postural drainage twice daily. The incidence of atelectasis, excluding small marginal atelectatic densities, which appear to be of little clinical significance and not affected by physiotherapy, was 13 per cent. In the other 100 cases, not treated with physiotherapy and used as a control, the incidence of atelectasis was 24 per cent. A drug to decrease the viscosity of the bronchial secretion was used in both groups, and this practice is recommended as a routine measure.

D. A. BREWERTON

The Life History of the Neuron. P. WEISS. *J. chron. Dis.*, 1956, **3**, 340.

The hitherto accepted concept of the neurone as a fixed structure, permanent from birth and incapable of development, has been revised. The neurone is now regarded as being in a constant state of degradation and renewal. Studies by means of isotopes indicate a rapid turnover in nerve-cell protoplasm. An analogy can be taken from the growth of the epidermis. The deepest layer divides and pushes cells outwards towards the surface, eventually to be shed. Whenever production exceeds need the epidermis gets thicker, and, conversely, when shedding outstrips production the skin gets thinner. This constant reproduction of specific cells can be compared to the single neurone. At the pole of the nerve cell the protoplasm is being constantly reproduced and then passed out along the neurone; and the size of the neurone at any one moment is a ratio between production and dissipation. This is the

fundamental process which is postulated by the author, who bases his conclusions on a study extending over six years of more than 100,000 nerve fibres.

After a nerve fibre is crushed the proximal stump issues a thin filamentous outgrowth which grows down the degenerated portion to the end-organ. This over a passage of time enlarges to the full calibre of the original fibre. To do this the protoplasmic mass must enlarge by one hundred times. If a constriction is put on the fibre distal to the crush and then the fibre is cut, the thin filament grows through the constriction and eventually an asymmetry develops between the proximal and distal parts of the fibre. The fibre swells on the proximal side of the constriction, indicating that the neurone has regrown from the cell outwards. As local metabolic consumption is greater than the replacement from the nerve cell through the constricted passage the distal neurone cannot under these circumstances attain its former calibre. What is supplied along the neurone is the finished product of the cell, not a flux of essential substances, enzymes, etc., for distal protein synthesis. The best evidence of this is to be seen when the constriction on a nerve fibre is removed. The distal part of the nerve fibre will then swell gradually to its former calibre. Such a released axonal flow occurs at the rate of several millimetres daily. As evidence for this the increased production of ammonia, indicating protein breakdown, at the distal end of the fibre is put forward. There appears to be a constant conveyor-belt of protoplasm to the periphery from the nerve cell. This concept is further supported by Hyden, who showed a high rate of nucleic acid synthesis around the nerve cell, and by Samuels, who by using labelled phosphoprotein showed the rate of progress down the nerve fibres to be 2 mm. daily.

Similarly, neurones disconnected from their normal stimuli degenerate—for example, the prevention of the post-natal increase in size of retinal cells by withholding light. There can be little doubt as to the relation between function and size. Qualitative changes also occur, for if some neurones are reconnected to strange end-organs adaptation of function can occur.

The mechanisms of this protoplasmic reproduction are obscure. Production probably results as an interaction between the genic structure of the nucleus and the cytoplasm, producing a type-specific protoplasm. Thus the true neurone keeps renewing its substance during life, and may undergo "maturation" changes, comparable to micro-organisms acquiring facility to metabolize unusual substrates.

E. N. COOMES

NOTICE

GUY'S HOSPITAL MEDICAL SCHOOL

DIPLOMA IN PHYSICAL MEDICINE—PART I

THE next course for this Diploma will commence on Tuesday, January 7, 1958. Full particulars may be obtained from the Physics Department, Guy's Hospital Medical School, London, S.E.1.